

Monitoring Non Alcoholic Fatty Liver and Type 2 Diabetes Reducement



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Abstract

Fatty liver, or hepatic steatosis, is a term that describes the buildup of fat in the liver. It's normal to have some fat in your liver, but too much can become a health problem. The liver is the second largest organ in the body. Its function is to process everything we eat or drink and filter any harmful substances from the blood. This process is interrupted if too much fat is in the liver. Fatty liver is when fat accounts for more than 5 to 10 percent of liver's weight

Nonalcoholic fatty liver disease NAFLD develops when the liver has difficulty breaking down fats, which causes a buildup in the liver tissue. The cause is not related to alcohol. NAFL is diagnosed when more than 10 percent of the liver is fat.

Keywords: Controlled Attenuation Parameter; Fatty Liver; Insulin Resistance; Non-Alcoholic Fatty Liver Disease; Pre-Diabetes; Type 2 Diabetes Mellitus

Introduction

NAFLD may contribute to prediabetes and type 2 diabetes. Because the liver plays such an important role in regulating the body's blood sugar, the buildup of fat in the vital organ makes it harder to control fasting glucose levels. It also makes the body more resistant to insulin, straining the pancreas and its beta cells and speeding up the arrival of type 2 diabetes. "When you get fatty liver, diabetes is harder to control,"

Nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes (T2DM) often coexist. The prevalence of NAFLD is 59.67% in T2DM patients. This results in adverse outcomes such as higher rates of mortality due to cirrhosis. NAFLD includes a spectrum of pathological conditions, which range from simple steatosis (NAFL), nonalcoholic steatohepatitis (NASH), cirrhosis and hepatocellular carcinoma.

Aim of the Study

My aim to do this research is to help diabetes type2 individuals or patients to cure their health issues and fatty liver people to reduce their disease's, can help them in reducing there health problem. Society will be benefitted by them.

Definition of Non Alcoholic Fatty Liver Disease

NAFLD is defined as hepatic steatosis diagnosed either by histology/imaging with macro vesicular steatosis in >5% of hepatocytes according to histological analysis or by proton density fat fraction or >5.6% as assessed by proton magnetic resonance spectroscopy (MRS) or quantitative fat/water selective magnetic resonance imaging (MRI) with no secondary cause for steatosis.

Secondary Causes of Nonalcoholic Fatty Liver Disease

Prevalence

NAFLD is a growing public health problem reaching epidemic proportions and is considered as the most common cause of chronic liver disease. The prevalence of NAFL is 31% by MRS and 12.2% by histology, of which 5% had NASH. The prevalence of NAFLD is 59.67% in T2DM whereas biopsy-proven NASH in asymptomatic T2DM patients with normal liver function tests (LFTs) is 20%. This suggests that serum liver enzymes are less indicative of the severity of intrahepatic fat accumulation and that the currently used "normal" reference values for serum liver enzymes need revision. Armstrong *et al.* estimated the prevalence of advanced fibrosis in asymptomatic T2DM to be around 5%–7%.

Type 2 Diabetes Mellitus

1. Metabolic syndrome
2. Obesity
3. Physical inactivity

4. A high-calorie diet, excess saturated fats, refined carbohydrates, sugar-sweetened beverages, a high fructose intake.
5. Obstructive sleep apnea.

Since NAFLD is closely linked to metabolic syndrome, it has been regarded as the hepatic manifestation of the syndrome.

Evaluating the risk for NAFLD is recommended in all patients with any component of metabolic syndrome as all components of the metabolic syndrome correlate with the degree of liver fat content and also vice versa.

NAFLD is a slowly progressive disease; however, in 20%, it progresses rapidly. Progression in NAFL to fibrosis Stage 1 is every 14 years and every 7 years in NASH, which is further increased in the presence of arterial hypertension. Cirrhosis and liver failure occurs in 11%–20% in NASH patients over 10–15 years.

There is a 2.2-fold increase in overall mortality in NAFLD with the most common cause of death being cardiovascular disease. Patients with NASH (but not NAFL) have an increased liver-related mortality rate with decompensate liver failure and HCC corresponding to 2%. The mortality rate of T2DM patients due to cirrhosis is more than twice the general population and patients with both NAFLD and T2DM. Furthermore, they tend to have a poor prognosis with higher rates of cirrhosis and mortality.

Pathological ectopic fat accumulation together with low-grade chronic inflammatory state in the liver, an organ that is not able to accumulate fat, is a manifestation of NAFLD. The risk of T2DM increases by 5-fold in these patients as a result of IR in hepatic, muscle, and adipose tissue. The risk of developing T2DM can be modified with improvement in NAFLD. As of today, there are no prediction models for the development of T2DM in individuals with NAFLD, and hence, a pragmatic approach would be an annual surveillance. The individual's risk of developing NAFLD is modified or increased by the presence of T2DM. One of the likely precursors for NAFLD and its further progression could be pre diabetes.

Cardiovascular events in NAFLD are increased by 1.87-fold in the presence of T2DM. NAFLD has been associated with increased carotid intima-media thickness, increased coronary artery calcium score, early left ventricular diastolic dysfunction, decreased myocardial perfusion, and reduced myocardial high-energy phosphate metabolism in patients with T2DM.

NAFLD is also known to increase micro vascular complications of diabetes such as chronic kidney disease and retinopathy. These pathological changes occur due to the release of pro-inflammatory, procoagulant, and pro-oxidant mediators, which result in hepatic/systemic IR, atherogenic dyslipidemia, and the release of fetuin-A, fibroblast growth factor-21, and retinol-binding protein-4 by liver. In the liver and skeletal muscle, fetuin-A binds and inhibits the insulin receptor tyrosine kinase, thus inhibiting insulin signal transduction, resulting in systemic and hepatic IR.

Patients with diabetes or prediabetes had progressive fibrosis when their serial biopsies were studied. It has also been suggested that the advanced forms of NAFLD such as NASH, advanced fibrosis, cirrhosis, and HCC occur more commonly in these patients. Those patients with worsening metabolic risk factors tend to have increased progression from NAFL to NASH and fibrosis. A clinical model which predicted NASH and advanced fibrosis in NAFLD patients with T2DM was developed by Bazick *et al.* in 2015 which had a better accuracy than the NAFLD fibrosis score with a specificity of 90.0% and a sensitivity of 56.8%. This model took the following parameters into account such as BMI, waist circumference, HbA1c, IR by homeostasis model assessment (HOMA), and serum levels of alanine amino transferase (ALT), aspartate aminotransferase (AST), albumin, and ferritin. Thus, it could diagnose the presence of NASH in 1249 patients. Increased levels of inflammatory biomarkers and hyperinsulinemia that increased the risk of HCC further strengthened the patho physiological link between T2DM and HCC. Thus, patients with NAFLD should be screened for metabolic syndrome and T2DM and vice versa. Elastography can be used as a tool for screening NAFLD in T2DM patients. Although there is growing evidence that NAFLD is closely associated with CAD/CKD in T2DM, whether a causal association exists needs to be established.

Pathophysiology

The main pathogenic mechanism of NAFLD is IR in the liver and extrahepatic tissues such as adipose tissue and skeletal muscle which act synergistically leading to systemic inflammation which causes the release of proatherogenic and nephrotoxic factors. There is an increased flux of free fatty acids (FFAs) to ectopic tissues due to an increased rate of lipolysis in the dysfunctional adipose tissue causing the muscle and liver to develop IR and apoptosis. Thus, the "lipotoxic state" in NASH results in hepatocyte necroinflammation.

There are three sources of triacylglycerol (TAG) which tends to accumulate in the liver: 59% of it is from circulating FFAs; de novo lipogenesis (DNL – the process in which carbohydrates are converted to lipids) contributes to 26%; and the rest 14% is from the diet. FFAs entering the portal circulation has one of the three fates: either to undergo β -oxidation; to undergo reesterification to TAG and get fluxed out as very low-density lipoprotein; or to get stored in the liver after re-esterification. DNL is further enhanced by IR. There is reduced rate of glycogen synthesis with increased rate of gluconeogenesis in NAFLD. The increase in intrahepatic glucose and resultant product of glycolysis pyruvate act as substrates for DNL which in turn increases the production of acetyl-CoA, which gets converted to malonyl-CoA contributing to DNL, instead of allowing it to enter the citric acid cycle. All the above contribute to hepatic steatosis. Increased FFA flux into the liver aggravates hepatic IR. The mechanism contributing to hepatic IR is the translocation of protein kinase C to the membrane compartment from the cytosol causing impaired activation of insulin receptor substrate –

phosphoinositol-3 kinase .Increased levels of ceramide in hepatocytes repress protein kinase B activity resulting in decreased insulin signaling . Oxidative stress, mitochondrial dysfunction, and circulating cytokines are the contributing factors for transition from simple steatosis to NASH, which then progresses to fibrosis. In addition, there is a second "hit" that causes the failure of hepatocytes to regenerate causing an increase in fibrosis.

Diagnosis

For the diagnosis of NAFLD, there should be no history of previous or ongoing significant alcohol consumption, no exposure to steatogenic medications or other causes of liver disease, such as viral hepatitis.

For a precise diagnosis of NAFLD, liver biopsy is the investigation of choice

1. Indications for liver biopsy in NAFLD include:
2. NAFLD patients at increased risk to have steatosis hepatitis and advanced fibrosis
3. The metabolic syndrome and NAFLD fibrosis score: patients at risk for steatohepatitis and advanced fibrosis
4. Suspected NAFLD in whom competing etiologies for hepatic steatosis and coexisting chronic liver diseases cannot be excluded.

Based on liver biopsy, staging of steatosis and fibrosis can be made by various scores such as NAFLD activity score (NAS), steatosis, activity, and fibrosis score.

Noninvasive imaging test for steatosis is ultrasound (USG) (preferred for first-line diagnosis which shows increased echogenicity)/MRI: proton density fat fraction and proton MRS or quantitative fat/water-selective MRI/fibroscan/CT. USG has a sensitivity of 84.8%, specificity of 93.6%, PPV of 77%, and NPV of 67%. Transient elastography (TE) can detect steatosis >10% in contrast to MRI which can detect steatosis as low as <1%. Another advantage of MRI is that it is not affected by obesity in contrast to TE whose sensitivity declines in patients with BMI >35 kg/m². Furthermore, it can screen for HCC at the same session. There are various steatosis scores which predict the presence, not the severity, of steatosis such as fatty liver index, Steato test, and NAFLD liver fat score.

However, imaging techniques are unable to differentiate between simple benign steatosis, NASH, and the degree of fibrosis, and they merely describe the presence of a "fatty liver."

Whenever imaging tools are not available or feasible (e.g., large epidemiological studies), serum biomarkers and scores can also be considered alternative for the diagnosis of steatosis with a 2- to 4-fold elevation of serum ALT and AST levels. However, it can be normal in 78% of the patients .Usually AST/ALT ratio is <1. However, it may increase as fibrosis advances .Furthermore, alkaline phosphatase and GGT levels may be elevated, but the serum bilirubin level, prothrombin time, and serum albumin level are normal, except in cirrhosis.

Based on clinical, biochemical, or imaging measures, one cannot distinguish NASH from steatosis. Therefore, cytokeratin-18 fragments (CK-

18) produced during cell death by caspases can be used with a 66% sensitivity and 82% specificity. However, it is not recommended in routine clinical practice. Other biomarkers for diagnosis of NASH include the following:

1. Other cell death markers (e.g., soluble Fas and intact CK-18)
2. Adipokines (e.g., adiponectin, tumor necrosis factor- α [TNF- α], interleukin-6, and adipocyte fatty acid-binding protein)
3. Metabolic markers (HOMA-IR and growth factor receptor 21)
4. Inflammatory markers (e.g., C-reactive protein [CRP]).

For the diagnosis of liver fibrosis, various scores can be used such as NAFLD fibrosis score, enhanced liver fibrosis score, Fibro test, BARD score (AST, ALT, BMI, Diabetes/Impaired Fasting Glucose), and FIB4 score .One of the useful diagnostic techniques in NAFLD is TE which relies on measuring velocity of 50 MHz shearwave passing through the liver which is converted to a stiffness score measured in kPa. It has a sensitivity, specificity, positive predictive value, negative predictive value and accuracy of 100%, 73.9%, 77.8%, 100%, and 86.4%, respectively, in predicting fibrosis in NAFLD. Other imaging modalities for fibrosis include acoustic radiation force impulse, shear wave elastography, and magnetic resonance elastography.

Management

There is a limitation for the use of therapeutic disease-modifying options in NAFLD.

The interventions for the management have an indirect effect through improvement in IR and glycemia and thus are used for the treatment of T2DM as well. Pharmacotherapy has to be reserved for those with highest risk for disease progression in NAFLD. Definitive clinical trials are limited. Some of the drugs such as ursodeoxycholic acids are not recommended for the treatment of NASH/NAFLD . In this discussion, only the treatment options useful in NAFLD and T2DM are included:

Lifestyle Modification

It has been recommended that 500–1000 kcal energy deficit is required to induce a weight loss of 500–1000 g/week. Mediterranean diet with high-protein intake reduces liver fat on H1-MRS, when compared with a low-fat, high-carbohydrate diet. Thus, a weight loss $\geq 7\%$ over 12 months causes NASH regression in 25% and steatosis regression in 40%. However, rapid weight loss can worsen LFT in NAFLD. Fructose-containing beverages and foods and saturated fatty acids should be avoided. It is also stated that alcohol intake should be below the risk threshold (i.e., <30 g for men; <20 g for women . Regular coffee consumption of 2–3 cups daily also is known to decrease the risk of hepatic fibrosis. A 150–200 min/week of moderate intensity aerobic physical activities in 3–5 sessions such as brisk walking, stationary cycling, and 3 times/week of 45 min of resistance training also have been mentioned to be useful. Exercise alone can reduce hepatic steatosis, but its ability to improve other aspects of liver histology however remains unknown.

Statins

The GREACE trial showed the safety of statins in NAFLD/NASH. In dyslipidemia, statins and other lipid-lowering agents are considered safe in NAFLD and NASH with improvement in histology. Although statin use is warranted in NASH cirrhosis, it should be avoided in decompensated cirrhosis..

NAFLD is considered as one of the CVD risk factors. In T2DM, cardiovascular risk tends to be underestimated. Algorithms used for traditional CVD risk calculation usually tend to underrate cardiovascular risk in T2DM and NAFLD . Since there is no available evidence to the contrary, a statin is required if estimated 10-year cardiovascular risk is >15%. In addition to the benefits statins have on lipids, there is an improvement in insulin sensitivity, decrease in production of advanced glycation endproducts (AGEs), and anti-inflammatory effects, which might reduce steatosis and inflammation associated with NASH. However, statin should not be used in NASH alone without the association of dyslipidemia till there is proven histological improvements as clinical trials on statins as treatment for NASH are limited and have shown inconsistent results.

Hypertriglyceridemia, which often coexists in NAFLD and T2DM, can be treated with high-dose omega-3 polyunsaturated fatty acid (PUFAs) . Their mechanism of action involves the activation of FGF21 which in turn activates peroxisome proliferator-activated receptor alpha (PPAR alpha) α , resulting in activation of several genes involved in fatty acid oxidation . However, PUFAs cannot be considered to have a specific role in the treatment of NAFLD/NASH unless there is coexisting hypertriglyceridemia.

Oxidative stress occurs in both NAFLD and T2DM. According to PIVENS trial, 800 IU/day of Vitamin E for 96 weeks improved liver enzymes, steatosis, inflammation, and ballooning (except fibrosis) and induced resolution of NASH in 42% of patients. Consequently, it has been considered as a first-line pharmacotherapy at dose of 800 IU/day for nondiabetic adults with biopsy-proven NASH. Nevertheless, it has not been recommended in T2DM with NASH, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis unless further data supporting its effectiveness become available.

Pentoxifylline, a nonselective phosphodiesterase inhibitor, has a role in decreasing the inflammatory pathways such as TNF- α . Mixed results on plasma aminotransferases and hepatic steatosis on imaging have been established with some studies showing improvement while some showing no improvement.

Insulin

Although IR with hyperinsulinemia is deleterious to the liver, exogenous insulin in T2DM patients can be worthwhile. As NAFLD is closely linked with IR, there is an increased requirement of insulin, which has the potential for weight gain . T2DM patients inadequately controlled on oral antidiabetic drugs when put on 12 weeks of insulin glargine therapy had hepatic fat reduction on MRS by 12.6 % to 9.9% with an improvement in HbA1c from 7.9% to

7.2%. While insulin enhances lipogenesis with decrease in lipid oxidation *in vitro*, human studies show paradoxical improvement in liver fat, which could be attributed to increased TAG secretion, improved hepatic insulin sensitivity, and reduced gluconeogenesis. Thus, in T2DM and across all the stages of NAFLD, insulin is effective in optimizing glycemic control. Insulin has a profibrotic effect, causing proliferation of hepatic stellate cells and accumulation of type 1 collagen. Ryysy *et al.* concluded that intrahepatic triglyceride content was associated with high daily insulin dose and linked with IR.

Metformin is the first-line therapeutic agent in the treatment of T2DM .Metformin decreases body fat with an improvement in hepatic insulin sensitivity .Fatty acid oxidation is enhanced, and de novo lipogenesis is reduced secondary to activation of protein kinase without significant histological improvement in hepatic steatosis or inflammation .In NAFLD without diabetes, there is no license for the use of metformin. It has been stated that there is improved survival in cirrhosis and HCC even though definitive improvement in steatosis or histological features of NASH has not been established.

Role of sulfonylurea in NAFLD with diabetes has still not been established by prospective studies. On the contrary, retrospective data have suggested that T2DM with NAFLD treated with sulfonylureas has a higher risk of fibrosis due to the profibrotic effect of insulin.

Future Directions

The FLINT study showed that treatment with obeticholic acid which is a farnesoid X receptor activator resulted in modest benefit by suppressing the cholesterol 7 α hydroxylase, a rate limiting enzyme in bile acid synthesis from cholesterol. It also causes stimulation of PPAR gamma resulting in decreased levels of triglycerides. But until further safety and efficacy data are available, it is recommended not to use as an off-label drug to treat NASH. In GOLDEN 505 trial, elafibranor, a PPAR α/δ agonist, at a dose 120 mg for 1 year, resulted in combined benefits of lipid metabolism of a PPAR α and insulin sensitivity of PPAR δ agonist, but there was no resolution of NASH. However, histological benefits in patients with a higher NAS score (≥ 4) were reported with an improvement in cardiometabolic profile with a mild reversible increase in serum creatinine.

Other drugs that are in development are:

1. Dual chemokine receptor CCR2/CCR5 antagonists
2. Fatty acid/bile acid conjugates[
3. Antifibrotic agents (anti-lysyl oxidase-like [anti-LOXL2] monoclonal antibodies)
4. Phlebotomy: hepatic iron accumulation is associated with IR, and iron depletion improves IR
5. Caspase inhibitors.

Definition of Nonalcoholic Fatty Liver Disease

NAFLD is defined as hepatic steatosis diagnosed either by histology/imaging with macrovesicular steatosis in >5% of hepatocytes

according to histological analysis or by proton density fat fraction or >5.6% as assessed by proton magnetic resonance spectroscopy (MRS) or quantitative fat/water selective magnetic resonance imaging (MRI) with no secondary cause for steatosis.[3] Secondary causes of steatosis are included in Table 1.[4]

Table 1**Secondary Causes of Nonalcoholic Fatty Liver Disease Prevalence**

NAFLD is a growing public health problem reaching epidemic proportions and is considered as the most common cause of chronic liver disease. The prevalence of NAFL is 31% by MRS and 12.2% by histology, of which 5% had NASH. The prevalence of NAFLD is 59.67% in T2DM whereas biopsy-proven NASH in asymptomatic T2DM patients with normal liver function tests (LFTs) is 20%. This suggests that serum liver enzymes are less indicative of the severity of intrahepatic fat accumulation and that the currently used "normal" reference values for serum liver enzymes need revision. Armstrong *et al.* estimated the prevalence of advanced fibrosis in asymptomatic T2DM to be around 5%–7%.

Risk Factors for Nonalcoholic Fatty Liver Disease**Type 2 Diabetes Mellitus**

1. Metabolic syndrome
2. Obesity
3. Physical inactivity
4. A high-calorie diet, excess saturated fats, refined carbohydrates, sugar-sweetened beverages, a high fructose intake³
5. Obstructive sleep apnea.

Since NAFLD is closely linked to metabolic syndrome, it has been regarded as the hepatic manifestation of the syndrome. Evaluating the risk for NAFLD is recommended in all patients with any component of metabolic syndrome as all components of the metabolic syndrome correlate with the degree of liver fat content and also vice versa.

Natural history of nonalcoholic fatty liver disease

NAFLD is a slowly progressive disease; however, in 20%, it progresses rapidly.[1] Progression in NAFL to fibrosis Stage 1 is every 14 years and every 7 years in NASH, which is further increased in the presence of arterial hypertension.[11] Cirrhosis and liver failure occurs in 11%–20% in NASH patients[11] over 10–15 years.

There is a 2.2-fold increase in overall mortality in NAFLD with the most common cause of death being cardiovascular disease. Patients with NASH (but not NAFL) have an increased liver-related mortality rate with decompensated liver failure and HCC corresponding to 2%. The mortality rate of T2DM patients due to cirrhosis is more than twice the general population and patients with both NAFLD and T2DM. Furthermore, they tend to have a poor prognosis with higher rates of cirrhosis and mortality.

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in hepatic, muscle, and adipose tissue.[13] The risk of developing T2DM can be modified with improvement in NAFLD. As of today, there are no prediction models for the development of T2DM in individuals with NAFLD, and hence, a pragmatic approach would be an annual surveillance.

The individual's risk of developing NAFLD is modified or increased by the presence of T2DM. One of the likely precursors for NAFLD and its further progression could be prediabetes.

Nonalcoholic Fatty Liver Disease and Diabetes**The association**

Cardiovascular events in NAFLD are increased by 1.87-fold in the presence of T2DM. NAFLD has been associated with increased carotid intima-media thickness, increased coronary artery calcium score, early left ventricular diastolic dysfunction, decreased myocardial perfusion, and reduced myocardial high-energy phosphate metabolism in patients with T2DM.

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Patho Physiology

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synergistically leading to systemic inflammation which causes the release of proatherogenic and nephrotoxic factors. There is an increased flux of free fatty acids (FFAs) to ectopic tissues due to an increased rate of lipolysis in the dysfunctional adipose tissue causing the muscle and liver to develop IR and apoptosis. Thus, the "lipotoxic state" in NASH results in hepatocyte necroinflammation.

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Diagnosis

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1. For a precise diagnosis of NAFLD, liver biopsy is the investigation of choice
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 - ii. The metabolic syndrome and NAFLD fibrosis score: patients at risk for steatohepatitis and advanced fibrosis
 - iii. Suspected NAFLD in whom competing etiologies for hepatic steatosis and coexisting chronic liver diseases cannot be excluded.

Based on liver biopsy, staging of steatosis and fibrosis can be made by various scores such as NAFLD activity score (NAS), steatosis, activity, and fibrosis score.
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echogenicity)/MRI: proton density fat fraction and proton MRS or quantitative fat/water-selective MRI/fibroscan/CT.[3] USG has a sensitivity of 84.8%, specificity of 93.6%, PPV of 77%, and NPV of 67%. Transient elastography (TE) can detect steatosis >10% in contrast to MRI which can detect steatosis as low as <1%.[1] Another advantage of MRI is that it is not affected by obesity in contrast to TE whose sensitivity declines in patients with BMI >35 kg/m². Furthermore, it can screen for HCC at the same session. There are various steatosis scores which predict the presence, not the severity, of steatosis such as fatty liver index, Steato test, and NAFLD liver fat score.

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2. Adipokines (e.g., adiponectin, tumor necrosis factor- α [TNF- α], interleukin-6, and adipocyte fatty acid-binding protein)
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For the diagnosis of liver fibrosis, various scores can be used such as NAFLD fibrosis score, enhanced liver fibrosis score, Fibro test, BARD score (AST, ALT, BMI, Diabetes/Impaired Fasting Glucose), and FIB4 score. One of the useful diagnostic techniques in NAFLD is TE which relies on measuring velocity of 50 MHz shearwave passing through the liver which is converted to a stiffness score measured in kPa. It has a sensitivity, specificity, positive predictive value, negative predictive value and accuracy of 100%, 73.9%, 77.8%, 100%, and 86.4%, respectively, in predicting fibrosis in NAFLD.

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The interventions for the management have an indirect effect through improvement in IR and glycemia and thus are used for the treatment of T2DM as well. Pharmacotherapy has to be reserved for those with highest risk for disease progression in NAFLD. Definitive clinical trials are limited. Some of the drugs such as ursodeoxycholic acids are not recommended for the treatment of NASH/NAFLD. In this discussion, only the treatment options useful in NAFLD and T2DM are included:

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Statins

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Fatty Acid**Omega -3 Polyunsaturated Fatty Acid**

Hypertriglyceridemia, which often coexists in NAFLD and T2DM, can be treated with high-dose omega-3 polyunsaturated fatty acid (PUFAs). Their mechanism of action involves the activation of FGF21

which in turn activates peroxisome proliferator-activated receptor α (PPAR α), resulting in activation of several genes involved in fatty acid oxidation.[29] However, PUFAs cannot be considered to have a specific role in the treatment of NAFLD/NASH[4] unless there is coexisting hypertriglyceridemia.

Vitamin E

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Pentoxifylline, a nonselective phosphodiesterase inhibitor, has a role in decreasing the inflammatory pathways such as TNF- α . Mixed results on plasma aminotransferases and hepatic steatosis on imaging have been established with some studies showing improvement while some showing no improvement.

Insulin

Although IR with hyperinsulinemia is deleterious to the liver, exogenous insulin in T2DM patients can be worthwhile. As NAFLD is closely linked with IR, there is an increased requirement of insulin, which has the potential for weight gain. T2DM patients inadequately controlled on oral antidiabetic drugs when put on 12 weeks of insulin glargine therapy had hepatic fat reduction on MRS by 12.6 % to 9.9% with an improvement in HbA1c from 7.9% to 7.2%. While insulin enhances lipogenesis with decrease in lipid oxidation *in vitro*, human studies show paradoxical improvement in liver fat, which could be attributed to increased TAG secretion, improved hepatic insulin sensitivity, and reduced gluconeogenesis. Thus, in T2DM and across all the stages of NAFLD, insulin is effective in optimizing glycemic control.

Pentoxifylline

Insulin has a profibrotic effect, causing proliferation of hepatic stellate cells and accumulation of type 1 collagen. Ryysy *et al.* concluded that intrahepatic triglyceride content was associated with high daily insulin dose and linked with IR.

Metformin

Metformin is the first-line therapeutic agent in the treatment of T2DM. Metformin decreases body fat with an improvement in hepatic insulin sensitivity. Fatty acid oxidation is enhanced, and de novo lipogenesis is reduced secondary to activation of protein kinase without significant histological improvement in hepatic steatosis or inflammation. In NAFLD without diabetes, there is no license for the use of metformin. It has been stated that there is improved survival in cirrhosis and HCC even though

definitive improvement in steatosis or histological features of NASH has not been established.

Sulfonylurea

Role of sulfonylurea in NAFLD with diabetes has still not been established by prospective studies. On the contrary, retrospective data have suggested that T2DM with NAFLD treated with sulfonylureas has a higher risk of fibrosis due to the profibrotic effect of insulin.

Thiazolidinediones

Glitazones cause adipose tissue sensitization to insulin through activation of PPAR γ resulting in fatty acid uptake and storage. There is also an increase in adiponectin with amelioration of pro-inflammatory adipokines, thus reducing gluconeogenesis and fatty acid influx improving insulin sensitivity. They also cause restoration of normal adipose tissue biology and result in an improvement in hepatic steatosis. PIVENS trial compared low-dose pioglitazone versus Vitamin E versus placebo for 2 years in patients without overt diabetes and concluded that pioglitazone (improved all histological features [except for fibrosis]) and resolution of NASH was achieved more than placebo. Cusi *et al.* in a double-blind randomized placebo-controlled study concluded that reduction in NAS (incorporating the sum of improvement of hepatic steatosis, inflammation, and ballooning without worsening of fibrosis) was achieved with pioglitazone in NASH with prediabetes or T2DM. Improvement in fibrosis, insulin sensitivity in liver, skeletal muscle, and adipose tissue was also present; the positive outcomes were maintained even after 36 months of treatment. To sum up, it has a role in biopsy-proven NASH with T2DM. Nevertheless, NASH can recur off-therapy and thus continued treatment is mandatory. However, in nondiabetics with NAFLD, there is no approval by FDA for its use.

Dipeptidyl Peptidase Inhibitors

NASH patients have higher serum dipeptidyl peptidase IV (DDP-IV) as compared to controls with liver staining for DDP-IV correlating with histopathological grade.[48] In animal models of diet-induced obesity, DDP-IV inhibitors result in activating 5'-Adenosine monophosphate-activated protein kinase (AMPK) with downregulation of genes involved in lipogenesis, thus attenuating lipogenesis. In animal models of liver injury, amelioration of liver inflammation due to an improvement in insulin sensitivity and hepatic steatosis prevented the progression to fibrosis. DDP-IV inhibition resulted in an improved glycemic control with reduced AST and ALT in a small, nonrandomized study of individuals with ultrasonographic steatosis. Treatment with DDP-IV inhibitors for 6 months resulted in reduced hepatic triglyceride as measured by MRS in a prospective blinded randomized controlled study. At present, evidence to discriminate the use of different DDP-IV inhibitors for patients with coexistent NAFLD with diabetes is still lacking. It has to be used cautiously in patients with severe hepatic impairment.

Glucagon-Like Peptide-1 (GLP-1) Analogs

Glucagon-like peptide-1 (GLP-1) analogs can result in an improved hepatic steatosis and steatohepatitis by weight loss and by the expression of GLP-1 receptor as seen in animal studies.[49] GLP-1 agonists have a direct action to inhibit lipogenesis in hepatocytes resulting in an improvement in insulin action in hepatocytes and adipose tissue since the pathology in NAFLD involves DNL.

Incubation of hepatocytes with NASH with exenatide resulted in an increased peroxisome PPAR α expression causing reduced c-Jun N-terminal kinase phosphorylation.

This causes an increased insulin sensitization. In addition, there was an increased protein kinase A activity, Akt and AMPK phosphorylation, which resulted in protein kinase a-dependent increase in PPAR α activity. Liraglutide is found to be useful for those with NASH both with diabetes. In a placebo-controlled study, 39% of patients who received liraglutide had resolution of NASH compared to only 9% in the placebo arm at 52 weeks. However it is premature to consider GLP1 analogs to specifically treat NAFLD/NASH.

Sodium Glucose Cotransporter 2 Inhibitors

In animal models of NAFLD with sodium glucose cotransporter 2 inhibitors, a protective effect on steatosis, inflammation, and fibrosis was seen. Glycosuria by causing negative energy balance and substrate switching toward lipids as a source of energy expenditure can cause attenuation of steatosis–fibrosis progression. No human studies of SGLT2 inhibitors and NAFLD are available.

Bariatric Surgery

Indication for bariatric surgery is noncirrhotic NASH unresponsive to lifestyle changes and pharmacotherapy.[Clearance of NASH was seen in 85% of patients, and inflammation and fibrosis in 37% and 20%, respectively.[This was attributed to weight loss. The prevalence of metabolic syndrome reduced from 70% to 14%,i.e., there was a resolution of hypertension, dysglycemia, and dyslipidemia in 85%, 93.8%, and 95.6% of patients, respectively. Portal hypertension should be excluded before attempting surgery.

Mechanisms by which bariatric surgery improves NAFLD are as follows:

1. Decreasing ghrelin and increasing GLP-1, Pancreatic polypeptide γ (PPY), and oxyntomodulin, thereby enhancing insulin sensitivity and decreasing appetite
2. Decreasing inflammation by decreasing IL1, IL8, CRP, and TNF α
3. Improving dyslipidemia
4. Improving adiponectin level and decreasing the expression of hepatic factors involved in the progression of fibrosis and inflammation
5. Decreasing IR
6. Promoting weight loss.

Guidelines for follow-up in NAFLD patients[are shown in Table 2.

Table 2

Follow-up guidelines of nonalcoholic fatty liver disease

Future Directions

The FLINT study showed that treatment with obeticholic acid which is a farnesoid X receptor activator resulted in modest benefit by suppressing the cholesterol 7 α hydroxylase, a rate limiting enzyme in bile acid synthesis from cholesterol. It also causes stimulation of PPAR gamma resulting in decreased levels of triglycerides. But until further safety and efficacy data are available, it is recommended not to use as an off-label drug to treat NASH. In GOLDEN 505 trial, elafibranor, a PPAR α/δ agonist, at a dose 120 mg for 1 year, resulted in combined benefits of lipid metabolism of a PPAR α and insulin sensitivity of PPAR δ agonist, but there was no resolution of NASH. However, histological benefits in patients with a higher NAS score (≥ 4) were reported with an improvement in cardiometabolic profile[56] with a mild reversible increase in serum creatinine.

Other drugs that are in development are:

1. Dual chemokine receptor CCR2/CCR5 antagonists
2. Fatty acid/bile acid conjugates
3. Antifibrotic agents (anti-lysyl oxidase-like [anti-LOXL2] monoclonal antibodies)
4. Phlebotomy: hepatic iron accumulation is associated with IR, and iron depletion improves IR
5. Caspase inhibitors.

Conclusion

T2DM and NAFLD have a common association. The increasing prevalence makes it a public health problem. They influence the course of the other. In the presence of steatosis, immediate clinical investigation for features of metabolic syndrome, IR, and T2DM is required because of its close association with IR. Vice versa in patients with T2DM, evaluation of NAFLD or NASH is mandated. T2DM needs to be controlled effectively to reduce IR which can show an amelioration in the NAFL. The diagnosis and management of NAFLD in T2DM has many challenges that need to be addressed. The current gold standard of care involves tailoring a treatment strategy to optimize the metabolic control with the goal to improve liver phenotype. The causative mechanism driving NAFLD progression in T2DM and evaluating the results of newer antidiabetic treatments and identification of additional novel targets require future research.

resulting from secondary causes should be differentiated .

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Type 2 diabetes is different. The autoimmune systems of people with type 2 diabetes don't attack beta cells. Instead, type 2 diabetes is characterized by the body losing its ability to respond to insulin. This is known as insulin resistance.

The body compensates for the ineffectiveness of its insulin by producing more, but it can't always produce enough. Over time, the strain placed on the beta cells by this level of insulin production can destroy them, diminishing insulin production.

Non-alcoholic fatty liver disease (NAFLD) is the "Western" liver disease related to obesity, and forms part of the metabolic syndrome characterized by increased body mass index (BMI), hypertension and insulin resistance.

Nonalcoholic fatty liver disease is an increasingly recognized clinic pathological condition that may progress to end-stage liver disease. The pathological picture resembles alcohol-induced liver injury, but occurs in patients who do not abuse alcohol. This disease comprises a wide spectrum of liver damage, ranging from simple steatosis, to steatohepatitis, to advanced fibrosis and cirrhosis. Steatohepatitis (nonalcoholic) represents only a stage within the spectrum of nonalcoholic fatty liver disease. Nonalcoholic fatty liver disease and steatosis with or without hepatitis resulting from

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